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☐	L1	sohocki.in.	2

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S11071	U	PGPB,USPT	(aryl with hydrocarbon with receptor with interacting with protein with like) OR (AIPL1)	2006-08-24 18:46:51
S11070	U	PGPB,USPT	(aryl with hydrocarbon with receptor with interacting with protein with like) AND (AIPL1)	2006-08-24 18:46:30
S11069	U	PGPB,USPT	AIPL1	2006-08-24 18:46:18
S11068	U	PGPB,USPT	aryl with hydrocarbon with receptor with interacting with protein with like	2006-08-24 18:46:03
S11067	U	PGPB,USPT	trp278x and (20030022165.PN.)	2006-08-24 18:37:51
S11066	U	PGPB,USPT	20030022165.PN.	

AND CURRENT DISCOVER FILE IS DATED 26 JUNE 2006.

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FULL ESTIMATED COST 0.21 0.21

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E2 1 SOHOCKI MELANIE MICHELLE/AU
E3 0 --> SOHOCKI MELANIE?/AU
E4 2 SOHOCKI R/AU
E5 1 SOHODA T/AU
E6 2 SOHODE K/AU
E7 1 SOHODE KANEYUKI/AU

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E8            1     SOHODLER A/AU
E9            2     SOHOEL A/AU
E10           3     SOHOEL ANDERS/AU
E11           2     SOHOEL D C/AU
E12           3     SOHOEL E O/AU

=> e1 or e2
L1           41 "SOHOCKI MELANIE M"/AU OR "SOHOCKI MELANIE MICHELLE"/AU

=> dup rem l1
PROCESSING COMPLETED FOR L1
L2           21 DUP REM L1 (20 DUPLICATES REMOVED)

=> d ibib abs l2 1-21

L2   ANSWER 1 OF 21     MEDLINE on STN                    DUPLICATE 1
ACCESSION NUMBER:   2004369718     MEDLINE <<LOGINID::20060905>>
DOCUMENT NUMBER:    PubMed ID: 15249368
TITLE:              The phenotype of Leber congenital amaurosis in patients
                    with AIPL1 mutations.
AUTHOR:             Dharmaraj Sharola; Leroy Bart P; Sohocki Melanie M
                    ; Koenekoop Robert K; Perrault Isabelle; Anwar Khalid;
                    Khaliq Shagufta; Devi R Summathi; Birch David G; De Pool
                    Elaine; Izquierdo Natalio; Van Maldergem Lionel; Ismail
                    Mohammad; Payne Annette M; Holder Graham E; Bhattacharya
                    Shomi S; Bird Alan C; Kaplan Josseline; Maumenee Irene H
CORPORATE SOURCE:   Johns Hopkins Center for Hereditary Eye Diseases, Wilmer
                    Eye Institute, Johns Hopkins Medical Institutions,
                    Baltimore, MD 21287-9237, USA.. sdharmaraj@jhmi.edu
SOURCE:             Archives of ophthalmology, (2004 Jul) Vol. 122, No. 7, pp.
                    1029-37.
                    Journal code: 7706534. ISSN: 0003-9950.
PUB. COUNTRY:       United States
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH:        200408
ENTRY DATE:         Entered STN: 28 Jul 2004
                    Last Updated on STN: 7 Aug 2004
                    Entered Medline: 6 Aug 2004
```

AB OBJECTIVES: To describe the phenotype of Leber congenital amaurosis (LCA) in 26 probands with mutations in aryl hydrocarbon receptor interacting protein-like 1 protein (AIPL1) and compare it with phenotypes of other LCA-related genes. To describe the electroretinogram (ERG) in heterozygote carriers. METHODS: Patients with AIPL1-related LCA were identified in a cohort of 303 patients with LCA by polymerase chain reaction single-strand confirmational polymorphism mutation screening and/or direct sequencing. Phenotypic characterization included clinical and ERG evaluation. Seven heterozygous carrier parents also underwent ERG testing. RESULTS: Seventeen homozygotes and 9 compound heterozygotes were identified. The W278X mutation was most frequent (48% of alleles). Visual acuities ranged from light perception to 20/400. Variable retinal appearances, ranging from near normal to varying degrees of chorioretinal atrophy and intraretinal pigment migration, were noted. Atrophic and/or pigmentary macular changes were present in 16 (80%) of 20 probands. Keratoconus and cataracts were identified in 5 (26%) of 19 patients, all of whom were homozygotes. The ERG of a parent heterozygote carrier revealed significantly reduced rod function, while ERGs for 6 other carrier parents were normal. CONCLUSIONS: The phenotype of LCA in patients with AIPL1 mutations is relatively severe, with a maculopathy in most patients and keratoconus and cataract in a large subset. Rod ERG abnormalities may be present in heterozygous carriers of AIPL1 mutations.

CLINICAL RELEVANCE: Understanding and recognizing the phenotype of LCA may help in defining the course and severity of the disease. Identifying the gene defect is the first step in preparation for therapy since molecular diagnosis in LCA will mandate the choice of treatment.

L2 ANSWER 2 OF 21 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2004185148 MEDLINE <<LOGINID::20060905>>
DOCUMENT NUMBER: PubMed ID: 15081406
TITLE: Abolished interaction of NUB1 with mutant AIPL1 involved in Leber congenital amaurosis.
AUTHOR: Kanaya Koichi; Sohocki Melanie M; Kamitani Tetsu
CORPORATE SOURCE: Department of Internal Medicine, Medical School, The University of Texas-Houston Health Science Center, Houston, TX 77030, USA.
CONTRACT NUMBER: R01 DK56298 (NIDDK)
SOURCE: Biochemical and biophysical research communications, (2004 May 7) Vol. 317, No. 3, pp. 768-73.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200405
ENTRY DATE: Entered STN: 15 Apr 2004
Last Updated on STN: 20 May 2004
Entered Medline: 19 May 2004
AB Leber congenital amaurosis (LCA) is often considered the most severe inherited retinopathy, and AIPL1 was the fourth gene identified as associated with LCA. Although the function of AIPL1 is unknown, it has been reported to interact with NUB1. Here, we searched for a NUB1-binding site on AIPL1 and located it between amino acid residues 181 and 330 in AIPL1. Importantly, many LCA-associated mutations of AIPL1 have been found at this site. Hence, we hypothesized that the interaction between NUB1 and AIPL1 is affected in patients with LCA. To test this possibility, we used three different assays to investigate the interaction between NUB1 and the AIPL1 mutants associated with LCA. Some of the AIPL1 mutants did not interact with NUB1, suggesting that abolishment of this interaction is involved in the pathogenesis of LCA. Other AIPL1 mutants, however, did interact with NUB1, suggesting that other molecules are also involved in the pathogenesis.

L2 ANSWER 3 OF 21 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2004608278 MEDLINE <<LOGINID::20060905>>
DOCUMENT NUMBER: PubMed ID: 15582159
TITLE: Retinal degeneration in Aipl1-deficient mice: a new genetic model of Leber congenital amaurosis.
AUTHOR: Dyer Michael A; Donovan Stacy L; Zhang Jiakun; Gray Jonathan; Ortiz Angelica; Tenney Rebeca; Kong Jian; Allikmets Rando; Sohocki Melanie M
CORPORATE SOURCE: Department of Developmental Neurobiology, St. Jude Children's Research Hospital, Memphis, TN 38105, USA.. michael.dyer@stjude.org
SOURCE: Brain research. Molecular brain research, (2004 Dec 20) Vol. 132, No. 2, pp. 208-20.
Journal code: 8908640. ISSN: 0169-328X.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200501
ENTRY DATE: Entered STN: 8 Dec 2004
Last Updated on STN: 2 Feb 2005

Entered Medline: 31 Jan 2005

AB Leber congenital amaurosis (LCA) is the most severe inherited retinopathy, with the earliest age of onset. Because this currently incurable disease is present from birth and is a relatively rare disorder, the development of animal models that closely resemble the phenotype in patients is especially important. Our previous genetic analyses of LCA patients identified mutations in the aryl-hydrocarbon interacting protein-like 1 (AIPL1) gene. Here we present development of an animal model of AIPL1-associated LCA, the Aipl1-deficient mouse. Aipl1 is expressed at low levels throughout human and mouse retinal development and is rapidly upregulated as photoreceptors differentiate. The mouse displays rapid retinal degeneration and massive Muler cell gliosis, resembling the phenotype of the rd mouse, which is caused by a mutation in the gene for the beta-subunit of the rod-specific phosphodiesterase. We confirm that this phenotype is consistent with the human disease using electroretinograms, and document the disease pathogenesis by analyzing the development of all retinal cell types and synaptogenesis during retinal histogenesis. Ectopic expression of AIPL1 led to deregulated retinal progenitor cell proliferation and alterations in cell fate specification; however, no gross abnormalities of proliferation during retinal development were detected. Data from analysis of proliferation and cell fate specification during retinal development of Aipl1-deficient mice suggests that there may be redundancy or compensation for Aipl1 loss by other related proteins. Because this mouse model closely mimics the human retinopathy caused by homozygous mutations in this gene, it provides a preclinical model for testing therapies to rescue the vision of children whose blindness is caused by AIPL1 mutations.

L2 ANSWER 4 OF 21 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 2004500899 MEDLINE <<LOGINID::20060905>>
DOCUMENT NUMBER: PubMed ID: 15469903
TITLE: Purification, characterisation and intracellular localisation of aryl hydrocarbon interacting protein-like 1 (AIPL1) and effects of mutations associated with inherited retinal dystrophies.
AUTHOR: Gallon Victoria A; Wilkie Susan E; Deery Evelyne C; Newbold Richard J; Sohocki Melanie M; Bhattacharya Shomi S; Hunt David M; Warren Martin J
CORPORATE SOURCE: School of Biological Sciences, Queen Mary, University of London, Mile End Road, E1 4NS, UK.
SOURCE: Biochimica et biophysica acta, (2004 Oct 14) Vol. 1690, No. 2, pp. 141-9.
Journal code: 0217513. ISSN: 0006-3002.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200411
ENTRY DATE: Entered STN: 8 Oct 2004
Last Updated on STN: 19 Dec 2004
Entered Medline: 24 Nov 2004

AB Mutations in AIPL1 are associated with Leber Congenital Amaurosis (LCA), a major cause of childhood blindness, yet the cellular function of the encoded protein has yet to be fully elucidated. In order to investigate the biochemistry of AIPL1, we have developed a system for the expression of the recombinant protein in bacteria and its subsequent purification. The secondary structure and thermostability of wild-type and mutant proteins have been examined by circular dichroism (CD) spectroscopy. Some of the variants, notably W278X and P376S, had markedly different secondary structure compositions, indicating that the proteins had not folded properly, whilst W278X and T114I were particularly thermolabile. When eukaryotic cells were transfected with the AIPL1 expression constructs, we

show by immunofluorescence microscopy that wild-type protein is distributed throughout the nucleus and cytoplasm. Several of the mutants give similar results. With two of the disease-associated variants (W278X and A336Delta2), however, the protein remains in the cytoplasm in aggresome-like particles. These particles were shown to be ubiquitinated, indicating that the mutant protein had been tagged for proteosomal degradation. On this basis, we can conclude that wild-type protein is expressed in a soluble and folded manner, and that some of the disease-associated mutant proteins are nonfunctional because they are insoluble and are degraded by the cell. Other mutations appear to have a more localised effect on secondary structure, which does not result in insolubility or affect protein targeting, but reduces the stability of the protein at human body temperature.

L2 ANSWER 5 OF 21 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:77413 CAPLUS <<LOGINID::20060905>>
DOCUMENT NUMBER: 138:135203
TITLE: Mutations in the AIPL1 gene encoding an aryl receptor interacting protein homolog on chromosome 17p cause Leber congenital amaurosis 4
INVENTOR(S): Sohocki, Melanie M.; Daiger, Stephen P.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 65 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003022165	A1	20030130	US 2001-765061	20010117
PRIORITY APPLN. INFO.:			US 2001-765061	20010117

AB A gene expressed in the eye and pineal gland encoding an aryl-hydrocarbon receptor interacting protein-like 1 (AIPL1) and that appears to play a role in the etiol. of Leber congenital amaurosis is mapped and cloned and mutant alleles characterized. Leber congenital amaurosis (LCA) is the most severe form of inherited retinal dystrophy and the most frequent cause of inherited blindness in children. LCA is usually inherited in an autosomal recessive fashion, although rare dominant cases have been reported. One form of LCA, LCA4, maps to chromosome 17p13 and is genetically distinct from other forms of LCA. The inventors recently identified the gene associated with LCA4, AIPL1 (aryl-hydrocarbon receptor interacting protein-like 1) and identified three mutations that were the cause of blindness in five families with LCA. Identification of the role of the gene was by cloning and mapping and by pedigree studies.

L2 ANSWER 6 OF 21 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:204282 CAPLUS <<LOGINID::20060905>>
DOCUMENT NUMBER: 140:37579
TITLE: The inherited blindness associated protein AIPL1 interacts with the cell cycle regulator protein NUB1. [Erratum to document cited in CA138:118994]
AUTHOR(S): Akey, Dayna T.; Zhu, Xuemei; Dyer, Michael; Li, Aimin; Sorensen, Adam; Blackshaw, Seth; Fukuda-Kamitani, Taeko; Daiger, Stephen P.; Craft, Cheryl M.; Kamitani, Tetsu; Sohocki, Melanie M.
CORPORATE SOURCE: Department of Environmental Health, Center for Genome Information, University of Cincinnati, Cincinnati, OH, 45267, USA
SOURCE: Human Molecular Genetics (2003), 12(4), 451
CODEN: HMGEE5; ISSN: 0964-6906

PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In Figure 4, the left blot was transposed; the corrected figure is given.

L2 ANSWER 7 OF 21 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2004280241 MEDLINE <<LOGINID::20060905>>
DOCUMENT NUMBER: PubMed ID: 15180275
TITLE: Functional studies of AIPL1: potential role of AIPL1 in cell cycle exit and/or differentiation of photoreceptors.
AUTHOR: Akey Dayna T; Zhu Xuemei; Dyer Michael; Li Amin; Sorensen Adam; Fukada-Kamitani Taeko; Daiger Stephen P; Craft Cheryl; Kamitani Tetsu; Sohocki Melanie M
CORPORATE SOURCE: University of Cincinnati, Cincinnati, OH 45267, USA.
CONTRACT NUMBER: EY00395 (NEI)
EY03040 (NEI)
SOURCE: Advances in experimental medicine and biology, (2003) Vol. 533, pp. 287-95.
Journal code: 0121103. ISSN: 0065-2598.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200408
ENTRY DATE: Entered STN: 8 Jun 2004
Last Updated on STN: 5 Aug 2004
Entered Medline: 4 Aug 2004

L2 ANSWER 8 OF 21 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 2002648220 MEDLINE <<LOGINID::20060905>>
DOCUMENT NUMBER: PubMed ID: 12374762
TITLE: The inherited blindness associated protein AIPL1 interacts with the cell cycle regulator protein NUB1.
AUTHOR: Akey Dayna T; Zhu Xuemei; Dyer Michael; Li Aimin; Sorensen Adam; Blackshaw Seth; Fukuda-Kamitani Taeko; Daiger Stephen P; Craft Cheryl M; Kamitani Tetsu; Sohocki Melanie M
CORPORATE SOURCE: Center for Genome Information, Department of Environmental Health, University of Cincinnati, OH 45267, USA.
CONTRACT NUMBER: EY00395 (NEI)
EY03040 (NEI)
SOURCE: Human molecular genetics, (2002 Oct 15) Vol. 11, No. 22, pp. 2723-33.
Journal code: 9208958. ISSN: 0964-6906.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AI844804
ENTRY MONTH: 200303
ENTRY DATE: Entered STN: 5 Nov 2002
Last Updated on STN: 18 Mar 2003
Entered Medline: 17 Mar 2003
AB Mutations in the aryl hydrocarbon receptor-interacting protein-like 1 (AIPL1) gene have been found in patients with Leber congenital amaurosis (LCA), a severe, early-onset form of retinal degeneration. To determine the normal function of AIPL1 and to better understand how mutations in this gene cause disease, we performed a yeast two-hybrid screen to identify AIPL1-interacting proteins in the retina. One of the identified interacting proteins corresponds to NUB1 (NEDD8 Ultimate Buster 1), which is thought to control many biological events, especially cell cycle progression, by downregulating NEDD8 expression. The AIPL1-NUB1

interaction was verified by co-immunoprecipitation studies in Y79 retinoblastoma cells, demonstrating that this interaction occurs within cells that share a number of features with retinal progenitor cells. Furthermore, we examined the localization of the AIPL1 protein within developing and adult retinas, and found that AIPL1 is present in the developing photoreceptor layer of the human retina and within the photoreceptors of the adult retina. Similar to AIPL1, NUB1 is also expressed in the developing and adult retina. Therefore, it is possible that the early-onset form of retinal degeneration seen in LCA patients with AIPL1 mutations may be due to a defect in the regulation of cell cycle progression during photoreceptor maturation. These data raise the possibility that AIPL1 is important for appropriate photoreceptor formation during development and/or survival following differentiation.

L2 ANSWER 9 OF 21 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:282579 BIOSIS <<LOGINID::20060905>>
DOCUMENT NUMBER: PREV200100282579
TITLE: Autosomal dominant retinal degeneration and bone loss in patients with a 12-bp deletion in the CRX gene.
AUTHOR(S): Tzekov, Radouil T. [Reprint author]; Liu, Yuhui; Sohocki, Melanie M.; Zack, Donald J.; Daiger, Stephen P.; Heckenlively, John R.; Birch, David G.
CORPORATE SOURCE: California Vitreoretinal Center, Stanford Hospital and Clinics, 1225 Crane Street, Menlo Park, CA, 94025, USA rtzekov@stanford.edu
SOURCE: IOVS, (May, 2001) Vol. 42, No. 6, pp. 1319-1327. print.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 13 Jun 2001
Last Updated on STN: 19 Feb 2002

AB PURPOSE: To define the phenotypic expression of a deletion in the gene encoding the transcription factor CRX in a large, seven-generation, white family. METHODS: Fourteen affected individuals, all heterozygous for the Leu146del12 mutation in the cone-rod homeobox gene (CRX), and four nonaffected relatives from the same family were examined with visual function tests, and 10 underwent bone mineral density (BMD) measurement. RESULTS: The ability of the mutated CRX protein to transactivate rhodopsin promoter was decreased by approximately 25%, and its ability to react synergistically with neural retinal leucine zipper (NRL) was reduced by more than 30%. The affected members of the family had an autosomal dominant ocular condition most closely resembling Leber congenital amaurosis (LCA) with severe visual impairment at an early age. Depending on age, affected members showed varying degrees of significant visual acuity loss, elevated dark-adaptation thresholds, significantly reduced cone and rod electroretinogram (ERG) amplitudes, and progressive constriction of the visual fields, in most cases leading to complete blindness. Six affected members had reduced levels of BMD in the spine and the hip (osteopenia). Four affected female members who were receiving long-term hormonal replacement therapy (HRT) demonstrated normal values of BMD. CONCLUSIONS: This large deletion of the CRX gene is associated with a severe form of autosomal dominant retinal degeneration. Affected members not receiving HRT showed reduced BMD (osteopenia). This phenotype may reflect the abnormal influence of mutant CRX on both retinal and pineal development.

L2 ANSWER 10 OF 21 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN DUPLICATE 7
ACCESSION NUMBER: 2001:356432 BIOSIS <<LOGINID::20060905>>
DOCUMENT NUMBER: PREV200100356432
TITLE: Comparative analysis of aryl-hydrocarbon receptor interacting protein-like 1 (Aipl1), a gene associated with inherited retinal disease in humans.

AUTHOR(S): Sohocki, Melanie M. [Reprint author]; Sullivan, Lori S.; Tirpak, Dayna L.; Daiger, Stephen P.
CORPORATE SOURCE: Human Genetics Center, School of Public Health, Houston, TX, 77225-0334, USA
msohocki@sph.oth.tmc.edu
SOURCE: Mammalian Genome, (July, 2001) Vol. 12, No. 7, pp. 566-568. print.
CODEN: MAMGEC. ISSN: 0938-8990.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Aug 2001
Last Updated on STN: 19 Feb 2002

AB Mutations in AIPL1 cause Leber congenital amaurosis (LCA), the most severe form of inherited blindness in children; however, the function of this protein in normal vision remains unknown. To determine amino acid subsequences likely to be important for function, we have compared the protein sequence of several species. Sequence conservation is highest across the three Aipl1 tetratricopeptide (TPR) motifs and extends across the protein, except for a proline-rich amino acid sequence present only at the C-terminus of primate Aipl1. The length of the proline-rich region varies within primates; however, the length differences between human and primate Aipl1 do not correlate with evolutionary distance. These observations reinforce the importance of the TPR domains for function, the similarity of Aipl1 to a family of proteins that act as molecular chaperones, and the importance of comparative sequencing data for determination of whether AIPL1 sequence variants in patients are likely to cause retinopathy.

L2 ANSWER 11 OF 21 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN DUPLICATE 8
ACCESSION NUMBER: 2001:71225 BIOSIS <<LOGINID::20060905>>
DOCUMENT NUMBER: PREV200100071225
TITLE: Prevalence of mutations causing retinitis pigmentosa and other inherited retinopathies.
AUTHOR(S): Sohocki, Melanie M.; Daiger, Stephen P.; Bowne, Sara J.; Rodriguez, Joseph A.; Northrup, Hope; Heckenlively, John R.; Birch, David G.; Mintz-Hittner, Helen; Ruiz, Richard S.; Lewis, Richard A.; Saperstein, David A.; Sullivan, Lori S. [Reprint author]
CORPORATE SOURCE: Houston, TX, 77225-0334, USA
lsullivan@sph.uth.tmc.edu
SOURCE: Human Mutation, (2001) Vol. 17, No. 1, pp. 42-51. print.
ISSN: 1059-7794.
DOCUMENT TYPE: Article
LANGUAGE: English
OTHER SOURCE: Genbank-AF024711; Genbank-AF143222; Genbank-AF148864; Genbank-U49742
ENTRY DATE: Entered STN: 7 Feb 2001
Last Updated on STN: 15 Feb 2002

AB Inherited retinopathies are a genetically and phenotypically heterogeneous group of diseases affecting approximately one in 2000 individuals worldwide. For the past 10 years, the Laboratory for Molecular Diagnosis of Inherited Eye Diseases (LMDIED) at the University of Texas-Houston Health Science Center has screened subjects ascertained in the United States and Canada for mutations in genes causing dominant and recessive autosomal retinopathies. A combination of single strand conformational analysis (SSCA) and direct sequencing of five genes (rhodopsin, peripherin/RDS, RP1, CRX, and AIPL1) identified the disease-causing mutation in approximately one-third of subjects with autosomal dominant retinitis pigmentosa (adRP) or with autosomal dominant cone-rod dystrophy (adCORD). In addition, the causative mutation was identified in 15% of subjects with Leber congenital amaurosis (LCA). Overall, we report

identification of the causative mutation in 105 of 506 (21%) of unrelated subjects (probands) tested; we report five previously unreported mutations in rhodopsin, two in peripherin/RDS, and one previously unreported mutation in the cone-rod homeobox gene, CRX. Based on this large survey, the prevalence of disease-causing mutations in each of these genes within specific disease categories is estimated. These data are useful in estimating the frequency of specific mutations and in selecting individuals and families for mutation-specific studies.

L2 ANSWER 12 OF 21 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:438122 CAPLUS <<LOGINID::20060905>>
DOCUMENT NUMBER: 137:383251
TITLE: Functional analysis of AIPL1: A novel photoreceptor-pineal specific protein causing Leber congenital amaurosis and other retinopathies
AUTHOR(S): Sohocki, Melanie M.; Tirpak, Dayna L.; Craft, Cheryl M.; Daiger, Stephen P.
CORPORATE SOURCE: Human Genetics Center and Dept. of Ophthalmology and Visual Science, The Univ. of Texas, Houston, USA
SOURCE: New Insights into Retinal Degenerative Diseases, [Proceedings of the International Symposium on Retinal Degeneration], 9th, Durango, CO, United States, Oct. 9-14, 2000 (2001), Meeting Date 2000, 37-44. Editor(s): Anderson, Robert E.; LaVail, Matthew M.; Hollyfield, Joe G. Kluwer Academic/Plenum Publishers: New York, N. Y.
CODEN: 69CSG5; ISBN: 0-306-46679-1
DOCUMENT TYPE: Conference
LANGUAGE: English
AB A comparative sequencing of AIPL1 orthologs between mammalian species and yeast two-hybrid analyses were conducted to detect AIPL1-binding proteins. Results reveal a high degree of sequence conservation across AIPL1 proteins, at least within mammals, and reinforce the structural relation of AIPL1 to the Fkbp families of proteins, which function as mol. chaperones in steroid receptor signaling, heat shock responses, and immunosuppression. The increased sequence conservation within the tetratricopeptide motifs suggests an important role for these motifs in protein function. Moreover, the conservation of certain residues within the proline-rich region suggests that they may be important for primate AIPL1 function. Yeast two-hybrid analyses identified two potential AIPL1-interacting proteins, clone #7 which is homologous to a glucose metabolism gene on human 5q and clone #16, homologous to a gene on human 15p.
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 13 OF 21 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN DUPLICATE 9
ACCESSION NUMBER: 2000:333943 BIOSIS <<LOGINID::20060905>>
DOCUMENT NUMBER: PREV200000333943
TITLE: Prevalence of AIPL1 mutations in inherited retinal degenerative disease.
AUTHOR(S): Sohocki, Melanie M. [Reprint author]; Perrault, Isabelle; Leroy, Bart P.; Payne, Annette M.; Dharmaraj, Sharola; Bhattacharya, Shomi S.; Kaplan, Josseline; Maumenee, Irene H.; Koenekoop, Robert; Meire, Francoise M.; Birch, David G.; Heckenlively, John R.; Daiger, Stephen P. [Reprint author]
CORPORATE SOURCE: Human Genetics Center, School of Public Health, University of Texas-Houston Health Science Center, Houston, TX, 77225-0334, USA
SOURCE: Molecular Genetics and Metabolism, (June, 2000) Vol. 70, No. 2, pp. 142-150. print.

ISSN: 1096-7192.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 10 Aug 2000
Last Updated on STN: 7 Jan 2002

AB Leber congenital amaurosis (LCA) is the most severe form of inherited retinal dystrophy and the most frequent cause of inherited blindness in children. LCA is usually inherited in an autosomal recessive fashion, although rare dominant cases have been reported. One form of LCA, LCA4, maps to chromosome 17p13 and is genetically distinct from other forms of LCA. We recently identified the gene associated with LCA4, AIPL1 (aryl-hydrocarbon interacting protein-like 1) and identified three mutations that were the cause of blindness in five families with LCA. In this study, AIPL1 was screened for mutations in 512 unrelated pro-bands with a range of retinal degenerative diseases to determine if AIPL1 mutations cause other forms of inherited retinal degeneration and to determine the relative contribution of AIPL1 mutations to inherited retinal disorders in populations worldwide. We identified 11 LCA families whose retinal disorder is caused by homozygous or compound heterozygous AIPL1 mutations. We also identified affected individuals in two apparently dominant families, diagnosed with juvenile retinitis pigmentosa or dominant cone-rod dystrophy, respectively, who are heterozygous for a 12-bp AIPL1 deletion. Our results suggest that AIPL1 mutations cause approximately 7% of LCA worldwide and may cause dominant retinopathy.

L2 ANSWER 14 OF 21 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN DUPLICATE 10
ACCESSION NUMBER: 2000:190652 BIOSIS <<LOGINID::20060905>>
DOCUMENT NUMBER: PREV200000190652
TITLE: Mutations in a new photoreceptor-pineal gene on 17p cause Leber congenital amaurosis.
AUTHOR(S): Sohocki, Melanie M.; Bowne, Sara J.; Sullivan, Lori S.; Blackshaw, Seth; Cepko, Constance L.; Payne, Annette M.; Bhattacharya, Shomi S.; Khaliq, Shagufta; Mehdi, S. Qasim; Birch, David G.; Harrison, Wilbur R.; Elder, Frederick F.B.; Heckenlively, John R.; Daiger, Stephen P. [Reprint author]
CORPORATE SOURCE: Human Genetics Center, School of Public Health, The University of Texas-Houston Health Science Center, Houston, TX, USA
SOURCE: Nature Genetics, (Jan., 2000) Vol. 24, No. 1, pp. 79-83. print.
ISSN: 1061-4036.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 17 May 2000
Last Updated on STN: 4 Jan 2002

AB Leber congenital amaurosis (LCA, MIM 204000) accounts for at least 5% of all inherited retinal disease and is the most severe inherited retinopathy with the earliest age of onset. Individuals affected with LCA are diagnosed at birth or in the first few months of life with severely impaired vision or blindness, nystagmus and an abnormal or flat electroretinogram (ERG). Mutations in GUCY2D (reference 3), RPE65 (reference 4) and CRX (reference 5) are known to cause LCA, but one study identified disease-causing GUCY2D mutations in only 8 of 15 families whose LCA locus maps to 17p13.1 (reference 3), suggesting another LCA locus might be located on 17p13.1. Confirming this prediction, the LCA in one Pakistani family mapped to 17p13.1, between D17S849 and D17S960-a region that excludes GUCY2D. The LCA in this family has been designated LCA4 (reference 6). We describe here a new photoreceptor/pineal-expressed gene, AIPL1 (encoding aryl-hydrocarbon interacting protein-like 1), that maps within the LCA4

candidate region and whose protein contains three tetra-tricopeptide (TPR) motifs, consistent with nuclear transport or chaperone activity. A homozygous nonsense mutation at codon 278 is present in all affected members of the original LCA4 family. AIPL1 mutations may cause approximately 20% of recessive LCA, as disease-causing mutations were identified in 3 of 14 LCA families not tested previously for linkage.

L2 ANSWER 15 OF 21 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:604884 CAPLUS <<LOGINID::20060905>>
DOCUMENT NUMBER: 132:19385
TITLE: Identification and evaluation of candidate genes for inherited retinal degenerative diseases
AUTHOR(S): Sohocki, Melanie Michelle
CORPORATE SOURCE: Health Science Center, Univ. of Texas, Houston, TX, USA
SOURCE: (1999) 76 pp. Avail.: UMI, Order No. DA9926496 From: Diss. Abstr. Int., B 1999, 60(4), 1419
DOCUMENT TYPE: Dissertation
LANGUAGE: English
AB Unavailable

L2 ANSWER 16 OF 21 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN DUPLICATE 11
ACCESSION NUMBER: 1999:483815 BIOSIS <<LOGINID::20060905>>
DOCUMENT NUMBER: PREV199900483815
TITLE: Mutations in the RP1 gene causing autosomal dominant retinitis pigmentosa.
AUTHOR(S): Bowne, Sara J.; Daiger, Stephen P.; Hims, Matthew M.; Sohocki, Melanie M.; Malone, Kimberly A.; McKie, Arthur B.; Heckenlively, John R.; Birch, David G.; Inglehearn, Chris F.; Bhattacharya, Shomi S.; Bird, Alan; Sullivan, Lori S. [Reprint author]
CORPORATE SOURCE: Human Genetics Center, School of Public Health, and Department of Ophthalmology and Visual Science, University of Texas-Houston Health Science Center, Houston, TX, 77225-0334, USA
SOURCE: Human Molecular Genetics, (Oct., 1999) Vol. 8, No. 11, pp. 2121-2128. print.
ISSN: 0964-6906.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 16 Nov 1999
Last Updated on STN: 16 Nov 1999
AB Retinitis pigmentosa is a genetically heterogeneous form of retinal degeneration that affects apprx1 in 3500 people worldwide. Recently we identified the gene responsible for the RP1 form of autosomal dominant retinitis pigmentosa (adRP) at 8q11-12 and found two different nonsense mutations in three families previously mapped to 8q. The RP1 gene is an unusually large protein, 2156 amino acids in length, but is comprised of four exons only. To determine the frequency and range of mutations in RP1 we screened probands from 56 large adRP families for mutations in the entire gene. After preliminary results indicated that mutations seem to cluster in a 442 nucleotide segment of exon 4, an additional 194 probands with adRP and 409 probands with other degenerative retinal diseases were tested for mutations in this region alone. We identified eight different disease-causing mutations in 17 of the 250 adRP probands tested. All of these mutations are either nonsense or frameshift mutations and leadto a severely truncated protein. Two of the eight different mutations, Arg677X and a 5 bp deletion of nucleotides 2280-2284, were reported previously, while the remaining six mutations are novel. We also identified two rare missense changes in two other families, one new polymorphic amino acid substitution, one silent substitution and a rare variant in the

5'-untranslated region that is not associated with disease. Based on this study, mutations in RP1 appear to cause at least 7% (17/250) of adRP. The 5 bp deletion of nucleotides 2280-2284 and the Arg677X nonsense mutation account for 59% (10/17) of these mutations. Further studies will determine whether missense changes in the RP1 gene are associated with disease, whether mutations in other regions of RP1 can cause forms of retinal disease other than adRP and whether the background variation in either the mutated or wild-type RP1 allele plays a role in the disease phenotype.

L2 ANSWER 17 OF 21 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN DUPLICATE 12

ACCESSION NUMBER: 1999:288844 BIOSIS <<LOGINID::20060905>>
DOCUMENT NUMBER: PREV199900288844
TITLE: Localization of retina/pineal-expressed sequences: Identification of novel candidate genes for inherited retinal disorders.
AUTHOR(S): Sohocki, Melanie M.; Malone, Kimberly A.; Sullivan, Lori S.; Daiger, Stephen P. [Reprint author]
CORPORATE SOURCE: Human Genetics Center, University of Texas Health Science Center, Houston, TX, 77225-0334, USA
SOURCE: Genomics, (May 15, 1999) Vol. 58, No. 1, pp. 29-33. print. CODEN: GNMCEP. ISSN: 0888-7543.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Aug 1999
Last Updated on STN: 5 Aug 1999

AB More than 100 genes causing inherited retinal diseases have been mapped to chromosomal locations, but less than half of these genes have been cloned. Mutations in many retina/pineal-specific genes are known to cause inherited retinal diseases. Examples include mutations in arrestin, rhodopsin kinase, and the cone-rod homeobox gene, CRX. To identify additional candidate genes for inherited retinal disorders, novel retina/pineal-expressed EST clusters were identified from the TIGR Human Gene Index database and mapped to specific chromosomal sites. After known human gene sequences were excluded, and repeat sequences were masked, 26 novel retina and pineal gland cDNA clusters were identified. The retinal expression of each novel EST cluster was confirmed by PCR assay of a retinal cDNA library, and each cluster was localized in the genome using the GeneBridge 4.0 radiation hybrid panel. In silico expression data from the TIGR database suggest that these EST clusters are retina/pineal-specific or predominantly expressed in these tissues. This combination of database analysis and laboratory investigation has localized several EST clusters that are potential candidates for genes causing inherited retinopathy.

L2 ANSWER 18 OF 21 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN DUPLICATE 13

ACCESSION NUMBER: 2000:102316 BIOSIS <<LOGINID::20060905>>
DOCUMENT NUMBER: PREV200000102316
TITLE: Identifying and mapping novel retinal-expressed ESTs from humans.
AUTHOR(S): Malone, Kimberly; Sohocki, Melanie M.; Sullivan, Lori S.; Daiger, Stephen P. [Reprint author]
CORPORATE SOURCE: Human Genetics Center, School of Public Health, Houston, TX, 77225-0334, USA
SOURCE: Molecular Vision, (May 4, 1999) Vol. 5, No. 5 CITED NOV. 18, 1999. print.
ISSN: 1090-0535.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 22 Mar 2000

Last Updated on STN: 3 Jan 2002

AB Purpose: The goal of this study was to develop efficient methods to identify tissue-specific expressed sequence tags (ESTs) and to map their locations in the human genome. Through a combination of database analysis and laboratory investigation, unique retina-specific ESTs were identified and mapped as candidate genes for inherited retinal diseases. Methods: DNA sequences from retina-specific EST clusters were obtained from the TIGR Human Gene Index Database. Further processing of the EST sequence data was necessary to ensure that each EST cluster represented a novel, non-redundant mapping candidate. Processing involved screening for homologies to known genes and proteins using BLAST, excluding known human gene sequences and repeat sequences, and developing primers for PCR amplification of the gene encoding each cDNA cluster from genomic DNA. The EST clusters were mapped using the GeneBridge 4.0 Radiation Hybrid Mapping Panel with standard PCR conditions. Results: A total of 83 retinal-expressed EST clusters were examined as potential novel, non-redundant mapping candidates. Fifty-five clusters were mapped successfully and their locations compared to the locations of known retinal disease genes. Fourteen EST clusters localize to candidate regions for inherited retinal diseases. Conclusions: This pilot study developed methodology for mapping uniquely expressed retinal ESTs and for identifying potential candidate genes for inherited retinal disorders. Despite the overall success, several complicating factors contributed to the high failure rate (33%) for mapping EST-clustered sequences. These include redundancy in the sequence data, widely dispersed sequences, ambiguous nucleotides within the sequences, the possibility of amplifying through introns and the presence of repetitive elements within the sequence. However, the combination of database analysis and laboratory mapping is a powerful method for identification of candidate genes for inherited diseases.

L2 ANSWER 19 OF 21 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN DUPLICATE 14

ACCESSION NUMBER: 1999:299941 BIOSIS <<LOGINID::20060905>>
DOCUMENT NUMBER: PREV199900299941
TITLE: A range of clinical phenotypes associated with mutations in CRX, a photoreceptor transcription-factor gene.
AUTHOR(S): Sohocki, Melanie M.; Sullivan, Lori S.; Mintz-Hittner, Helen A.; Birch, David; Heckenlively, John R.; Freund, Carol L.; McInnes, Roderick R.; Daiger, Stephen P. [Reprint author]
CORPORATE SOURCE: Human Genetics Center, University of Texas Health Science Center, Houston, TX, 77225-0334, USA
SOURCE: American Journal of Human Genetics, (Nov., 1998) Vol. 63, No. 5, pp. 1307-1315. print.
CODEN: AJHGAG. ISSN: 0002-9297.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 12 Aug 1999
Last Updated on STN: 12 Aug 1999

AB Mutations in the retinal-expressed gene CRX (cone-rod homeobox gene) have been associated with dominant cone-rod dystrophy and with de novo Leber congenital amaurosis. However, CRX is a transcription factor for several retinal genes, including the opsins and the gene for interphotoreceptor retinoid binding protein. Because loss of CRX function could alter the expression of a number of other retinal proteins, we screened for mutations in the CRX gene in probands with a range of degenerative retinal diseases. Of the 294 unrelated individuals screened, we identified four CRX mutations in families with clinical diagnoses of autosomal dominant cone-rod dystrophy, late-onset dominant retinitis pigmentosa, or dominant congenital Leber amaurosis (early-onset retinitis pigmentosa), and we identified four additional benign sequence variants. These findings imply

that CRX mutations may be associated with a wide range of clinical phenotypes, including congenital retinal dystrophy (Leber) and progressive diseases such as cone-rod dystrophy or retinitis pigmentosa, with a wide range of onset.

L2 ANSWER 20 OF 21 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:148631 CAPLUS <<LOGINID::20060905>>
DOCUMENT NUMBER; 128:253452
TITLE: Progress in positional cloning of RP10 (7q31.3), RP1 (8q11-q21), and VMD1 (8q24)
AUTHOR(S): Daiger, Stephen P.; McGuire, Rachel E.; Sullivan, Lori S.; Sohocki, Melanie M.; Blanton, Susan H.; Humphries, Peter; Green, Eric D.; Mintz-Hittner, Helen; Heckenlively, John R.
CORPORATE SOURCE: Human Genetics Center School of Public Health, USA
SOURCE: Degenerative Retinal Diseases, [Proceedings of the International Symposium on Retinal Degeneration], 7th, Sendai, Oct. 5-9, 1996 (1997), Meeting Date 1996, 277-289. Editor(s): LaVail, Matthew M.; Hollyfield, Joe G.; Anderson, Robert E. Plenum: New York, N. Y. CODEN: 65SSAH
DOCUMENT TYPE: Conference
LANGUAGE: English
AB The goal of this research is to determine the genes and mutations causing autosomal dominant retinitis pigmentosa (adRP) and related diseases. Three interrelated approaches are used, first, mutation screening in individual patients for mutations in rhodopsin or peripherin/RDS; second, linkage testing in adRP families without known mutations; and third, positional cloning of two mapped adRP genes, the RP10 locus on 7q31.3 and the RP1 locus on 8q11-q21. In addition, the authors are engaged in positional cloning of a dominant disease locus previously mapped close to the RP1 locus, atypical vitelliform macular degeneration (VMD1). This paper summarizes progress in each of these areas, with particular emphasis on positional cloning.
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 21 OF 21 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN DUPLICATE 15
ACCESSION NUMBER: 1997:180325 BIOSIS <<LOGINID::20060905>>
DOCUMENT NUMBER: PREV199799472038
TITLE: Human glutamate pyruvate transaminase (GTP): Localization to 8q24.3 cDNA and genomic sequences, and polymorphic sites.
AUTHOR(S): Sohocki, Melanie M.; Sullivan, Lori S.; Harrison, Wilbur R.; Sodergren, Erica J.; Elder, Frederick F. B.; Weinstock, George; Tanase, Sumio; Daiger, Stephen P. [Reprint author]
CORPORATE SOURCE: Human Genet. Cent., Sch. Public Health, Univ. Texas Health Sci. Cent., PO Box 20334, Houston, TX 77225-0334, USA
SOURCE: Genomics, (1997) Vol. 40, No. 2, pp. 247-252. CODEN: GNMCEP. ISSN: 0888-7543.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Apr 1997
Last Updated on STN: 24 Apr 1997
AB Two frequent protein variants of glutamate pyruvate transaminase (GPT) (E.C.2.6.1.2) have been used as genetic markers in humans for more than two decades, although chromosomal mapping of the GPT locus in the 1980s produced conflicting results. To resolve this conflict and develop useful DNA markers for this gene, we isolated and characterized cDNA and genomic clones of GPT. We have definitively mapped human GPT to the terminus of

Sq using several methods. First, two cosmids shown to contain the GPT sequence were derived from a chromosome 8-specific library. Second, by fluorescence in situ hybridization, we mapped the cosmid containing the human GPT gene to chromosome band 8q24.3. Third, we mapped the rat gpt cDNA to the syntenic region of rat chromosome 7. Finally, PCR primers specific to human GPT amplify sequences contained within a "half-YAC" from the long arm of chromosome 8, that is, a YAC containing the 8q telomere. The human GPT genomic sequence spans 2.7 kb and consists of 11 exons, ranging in size from 79 to 243 bp. The exonic sequence encodes a protein of 495 amino acids that is nearly identical to the previously reported protein sequence of human GPT-1. The two polymorphic GPT isozymes are the result of a nucleotide substitution in codon 14, coding for a histidine in GPT-1 and an asparagine in GPT-2, which causes a gain or loss of an NlaIII restriction site. In addition, a cosmid containing the GPT sequence also contains a previously unmapped, polymorphic microsatellite sequence, D8S421. The cloned GPT gene and associated polymorphisms will be useful for linkage and physical mapping of disease loci that map to the terminus of 8q, including atypical vitelliform macular dystrophy (VMD1) and epidermolysis bullosa simplex, type Ogna (EBS1). In addition, this will be a useful system for characterizing the telomeric region of 8q. Finally, determination of the molecular basis of the GPT isozyme variants will permit PCR-based detection of this worldwide polymorphism.

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